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Original research

A retrospective study examining thrombolysis for occluded femoro-popliteal grafts – Is it worthwhile?

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ABSTRACT

Aim: To assess the effectiveness of catheter directed thrombolysis (CDT) in the treatment of acute graft occlusion.
Methods: Tissue prothrombin activator (rt-PA) was the sole agent used for thrombolysis. This was infused through a 4F straight 65 cm catheter placed under ultrasound guidance. Following a pre-CDT angiogram, a catheter was placed just proximal to the distal anastomosis. An infusion of rt-PA was given over 24 h. An assessment of acute clinical success, limb salvage rates, patency rates and complication rates were made over a period of one year.
Results: 80% (20/25) of grafts were successfully reopened immediately. 4/5 (80%) of the unsuccessful CDT cases required amputation within a few weeks. 60% (12/20) of successful CDT cases had an underlying stenotic lesion which required angioplasty. Limb salvage rate was 72% (18/25) at 12 months. There was no CDT related mortality. Secondary patency rate at 9 months was 76% (13/17).
Conclusion: CDT can achieve reasonable results in this group of challenging patients and may be seen as a useful accessory in the vascular toolkit. However, precise indications for its use need further clarification.

1. Introduction

The precise indication in clinical practice for thrombolytic therapy in the management of acute limb ischaemia remains equivocal. The theoretical advantages are clear; they include the potential to reopen occluded vessels or grafts in situ, occluded collaterals and run-off. Further advantages include the unmasking of underlying anatomical pathology which may be amenable to endovascular or limited surgical intervention, limiting the trauma to endothelium and the gradual reintroduction of oxygen rich blood thus minimising reperfusion injuries. It has been shown that thrombolytic agents have the potential to limit skeletal muscle damage after critical ischaemia and may be due to controlled reperfusion of the microvasculature.[1] The main concern surrounds the reported long-term patency rates and the risk of systemic haemorrhage especially intra-cerebral haemorrhage. This argument may be justified as the initial use of intravenous (IV) thrombolysis for peripheral arterial occlusions (PAO) was followed by an extraordinarily high rate of bleeding complications,[2,3] with a reported mortality of 7%. Reports followed suggesting that intra-arterial (IA) thrombolysis may be a better modality of treatment for PAO with reduced risks of systemic bleeding.

The technique of IA catheter directed thrombolysis (CDT) was reported by Dotter et al. in 1974.[4] It was followed by widespread enthusiasm in the published literature during the 1980s. Early indications were that CDT was safe, offered a better limb salvage and mortality rate compared to surgery in the treatment of acute lower limb ischaemia (defined as symptom onset of less than 14 days).[5] Bleeding complications were more common in CDT patients but were relatively minor. In the aforementioned meta-analysis, the incidence of cerebrovascular accidents appeared to be 10 times more likely in surgical revascularizations.[6] Berridge et al.[7] had more trials available to them in their meta-analysis and found no significant difference in mortality or limb salvage rates between surgery and thrombolysis, but a slightly higher rate of significant bleeding complications in the thrombolysis group. Despite these findings, the use of IA thrombolysis in the treatment of acute limb ischaemia is not widely accepted. Some surgeons never consider it as an option. Concerns about its efficacy, cost, safety and long-term patency rates in reopened grafts remain.

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Urokinase was the agent used in most of the large studies analysed in the meta-analysis. However it was withdrawn by the US food and drug agency (FDA) in 1999 because of the potential to transmit infectious agents. Streptokinase has the disadvantage of being antigenic and can only be used once per patient. Moreover, both urokinase and streptokinase are relatively non-fibrin specific, acting on both circulating and fibrin bound prothrombin. In theory, this non-specificity may increase the risk of causing systemic fibrinolysis and bleeding. There has therefore been a shift to the genetically engineered and relatively more "fibrin-specific" agents. When used intra-arterially, these caused less systemic complications, decreased time to lysis and had lower dosage requirements.[8,9]

We have undertaken a retrospective analysis to review the results of CDT in our patients because initial inspection suggests that CDT should be considered more seriously as a viable and sometimes better alternative to surgical intervention.

2. Materials and methods

This is a retrospective analysis of patients treated with CDT at the St Peters hospital, Chertsey from February 2005 to April 2008. The authors mainly use thrombolysis in the management of failed or failing synthetic grafts. The interval corresponds to the time in which the same surgeon and radiologist have been working together on CDT. Recombinant tissue prothrombin activator (rt-PA) was the only agent used, and the same protocol for CDT has been adhered to during the period analysed. A thorough search of the computerised databases of the hospital (PACS, PAS and angiography suite records) was made using the keywords "thrombolysis" and "grafts" to identify all the patients that had undergone CDT in the hospital. Twenty three patients were identified (25 limbs/grafts). There were twenty one polytetraflouroethylene (PTFE) femoro-popliteal grafts, three PTFE ilio-popliteal grafts, and one silver coated Dacron axillo-popliteal graft. The case notes were reviewed and demographic data extracted. These included age, sex, duration of symptoms prior to lysis, and significant co-morbidities (hypertension, Diabetes Mellitus, renal failure and cardiac disease). The usual selection criteria for the use of thrombolysis in our hospital are acute symptoms of graft occlusion (symptoms less than 14 days) with an SVS/ISCVS (Society for vascular surgery/International society for cardiovascular surgery) grade of II.[10] However all patients that had undergone thrombolysis were included in this review including 2 patients that had symptoms lasting three weeks and four weeks. Patients with irreversible limb ischaemia and those with absolute contraindications to thrombolysis (Stroke, intracranial tumours, gastrointestinal haemorrhage in the last three months) were not offered thrombolysis. Follow up data was then extracted. Clinical findings and duplex scan results were obtained at approximately 3 months, 6 months and 12 months.

2.1. CDT procedure

The regime used for thrombolysis in our hospital was developed and standardised prior to the period of study. Fully informed consent was obtained before the procedure. A baseline haemoglobin estimation, white cell count, platelet count, clotting screen and renal function tests was obtained. Serum was saved for blood grouping. The patient was transferred to the angiography suite for the procedure. Intravenous antibiotics were given and maintained for the duration of thrombolysis. Prior to thrombolysis an angiogram was performed to confirm the graft occlusion and assess the outflow. Under ultrasound control, the thrombosed graft was punctured in an antegrade manner just below the proximal anastomosis. A guide wire and 4F straight 65 cm catheter (Cook, Bloomington, USA) was introduced with the distal end of the catheter lying just proximal to the distal anastomosis. If the popliteal artery was occluded then angioplasty was undertaken immediately in an attempt to open the popliteal artery. This angioplasty included the distal anastomosis. If the popliteal artery was patent, immediate angioplasty was not undertaken. The rationale for immediate angioplasty of the thrombosed popliteal artery was that limb salvage was expected to be poor in the presence of both femero-popliteal graft occlusion and popliteal artery occlusion. It was important to re-establish popliteal artery flow to improve the likelihood of both graft and limb salvage. Recombinant tissue plasminogen activator (rt-PA) was used for thrombolysis. A bolus dose of 5 mg rt-PA was given via the catheter over 5 min and maintained with an infusion of rt-PA at 1 mg/h. Analgesia was prescribed and the patient warned that there will be pain on reperfusion. The patient was observed in the surgical high dependency unit and the infusion continued for 24 h at which point a follow up angiogram was undertaken. During this angiogram, any underlying stenosis at the distal anastomosis underwent angioplasty. Lysis was usually complete in 24 h. The recommendation by Khosla et al.[11] in their study was never to exceed a total rt-PA dose of 100 mg as bleeding complications were more likely to occur then. On extraction of the catheter, an Angioseal© (St Jude Medical, Zaventem, Belgium) device was used to close the puncture site. The patients were then commenced on intravenous heparin (24,000 units per 24 h). Patients with re-occluded grafts were started on warfarin (INR range 2.0–2.5).

2.2. Outcome measures

There were seven main areas examined by this review. These were: 1) acute clinical success rate defined as the number of times thrombolysis was clinically and radiologically successful in reopening the occluded graft. Radiological success was deemed to have taken place if 90% of the graft lumen was open, with adequate run-off. This included the use of angioplasty pre- or post-thrombolysis. This radiological success was also confirmed clinically with a viable, non threatened limb and Doppler signal in at least one of the distal run-off vessels. 2) Underlying stenosis rate: the number of times a significant stenosis was unmasked by thrombolysis, requiring angioplasty. 3) Primary assisted patency rate: Patency of the target vessel with additional angioplasty or surgery within two weeks of initial CDT. This includes any thrombolysis repeated within two weeks. Patency rates were recorded at 3, 6 and 9 months. 4) Secondary patency rate: If any extra intervention (thrombolysis, angioplasty or surgery) was required to keep the graft open after two weeks, then this was considered secondary patency. 5) Complications: These were vascular or non-vascular. Vascular complications were considered minor if they could be managed by conservative means. Those requiring surgical/endovascular intervention or blood transfusions were considered major. Compartment syndrome was documented as a complication if the patient developed sufficient symptoms to require a fasciotomy after CDT. 6) Limb salvage rate: The number of limbs saved as a result of CDT. 7) Mortality rate: Mortality was attributed to CDT if patient died of a CDT related complication. The overall mortality rate was then noted at 30 days and at 12 months.

2.3. Statistical analyses

This was carried out using graph-pad prism 5. Differences between demographic factors and graft related variables were identified using Fischer's exact test, with a two tail p value (alpha < 0.05) where appropriate.

3. Results

23 patients (25 limbs) underwent CDT for acute infra-inguinal prosthetic graft occlusions. 64% were men. Acute clinical success was achieved in 20 grafts. Of the 5 that failed CDT, 4 had an amputation because of non-reconstructable distal disease. The remaining patient was managed conservatively and remained mobile and asymptomatic during the course of the study. The patient demographics with CDT success rates are shown in Table 1. There was no statistical difference shown in the success rate of CDT, between the different groups compared. In total, CDT was successful in 80% of cases. An underlying stenosis, requiring angioplasty was uncovered

Table 1
Demographics for patients undergoing CDT with success rates.

	CDT success rate
Gender	
M: 16 (64%)	12/16 (75%)[a]
F: 9 (36%)	8/9 (88.8%)
Age at presentation (yrs): Mean = 65.56	
≤60: 8/25 (32%)	7/8 (87.5%)[a]
>60: 17/25 (68%)	13/17 (76.5%)
Graft age (mths): Mean = 20.04	
≤12: 11/25 (44%)	9/11 (81.8%)[a]
>12: 14/25 (56%)	11/14 (78.6%)
Symptom duration (days) Mean = 6.56	
<14: 22/25 (88%)	18/22 (81.8%)[a]
≥14: 3/25 (12%)	2/3 (66.6%)
Diabetes: 9/25 (36%)	
Hypertension: 15/25 (60%)	
Ischaemic heart disease: 7/25 (28%)	
Renal failure: 1/25 (4%)	
CDT total n (%)	25 (100)
Unsuccessful	5/25 (20)
Successful	20/25 (80)
No stenosis	8/20 (40)
Stenosis	12/20 (60)
Proximal	4/12 (33.3)
Distal	8/12 (66.6)

[a] Not statistically significant.

Table 2
Significant complications following CDT.

Complications	Rate	
Infection	1/25 (4%)	Graft infection after above Knee amputation (AKA)
Bleeding		
Major	4/25 (16%)	Required blood transfusions (2 after thrombectomy and surgical vascular access respectively)
Minor	6/25 (32%)	Minor haematomas
Compartment syndrome	2/25 (8%)	Had fasciotomies
Renal dysfunction	1/25 (4%)	Mild. Noted in one patient with diabetes, Ischaemic heart disease and hypertension

in 60% of successful CDT. The predominant lesion was a distal stenosis (66.6%) and there was no intra-graft stenosis noted.

Four main complications were noted during the period of this study. These were infection, bleeding, compartment syndrome and renal dysfunction. There were no observed episodes of embolic phenomena. One graft infection was noted after CDT failure resulting in an above knee amputation (AKA). This patient had an axillo-popliteal bypass graft and a previous aorto-bifemoral graft. When CDT failed to reopen the graft, an AKA was performed. Unfortunately the patient developed an infection in the residual graft and expired as a result of sepsis. We do not feel this infective episode was a result of CDT. Bleeding was the most common complication. These were mainly haematomas at the site of the catheter puncture. In 4/25 (16%) patients, the patient dropped their haemoglobin enough to require a blood transfusion. These patients were classified as having major complications. One of these patients had surgery to obtain access, while the other had a popliteal thrombectomy to obtain distal run-off after CDT. Two patients developed a compartment syndrome, requiring fasciotomies. There was one patient with a urea of 21 mg/dL and creatinine of 151 mg/dL. This patient had associated risk factors for renal disease (Table 2) and developed a significant haematoma after CDT. His renal dysfunction resolved on blood transfusion and rehydration.

The patency rates are shown in Table 3. Primary assisted patency rate was 15/18 (83.3%) at 3 months. This was followed by a gradual decline to 41% at 9 months. However, the secondary patency rate was 76.5% at 9 months. Secondary patency was maintained by repeated thrombolysis and angioplasty ± stent placement as required. There were three repeat CDT episodes in three different grafts, which successfully re-established patency over the course of the 9 months.

Table 4 shows limb salvage rates. In four of five patients, failure of thrombolysis resulted in amputation within a few weeks, giving a limb salvage rate of 84% at one month. 3 more limbs were lost over the year, giving a limb salvage rate of 72% at one year. The two deaths recorded during the course of the study occurred within 6 weeks of CDT, and followed surgery for re-occluded limbs. The mortality rate was 8% at one year.

4. Discussion

In infra-inguinal arterial occlusive disease requiring bypass grafts, autogenous vein grafts remain the gold standard to which alternatives may be compared. It has a reported secondary patency rate of over 80% and 75% at one and five years respectively.[12] However, in many cases surgeon preference or lack of adequate vein conduit leads to the use of synthetic grafts. Synthetic grafts have an acceptable but slightly inferior long-term patency rate, especially in bypasses to the popliteal artery proximal to the knee joint. This difference in patency rates does not translate to any significant difference in limb salvage rates.[13] A substantial number of these failed synthetic grafts present with limb threatening ischaemia (SVS/ISVS standards grade II) and is reported to occur in approximately 78% of cases.[14] Redo surgery can be difficult in this subset of patients, who are often poor surgical candidates. This results in significant morbidity and mortality. Any approach that could potentially avoid surgery or limit its scope; provide acceptable patency, morbidity and mortality rates, would be welcome.

Table 3
Patency rates.

	1° assisted Patency	2° Patency
At 3 months	15/18 (83.3%)	16/18 (88.9%)
At 6 months	11/17 (64.7%)	15/17 (88.2%)
At 9 months	7/17 (41.2%)	13/17 (76.5%)

Table 4
Limb salvage rate and mortality.

	1 month	12 months
Limb Salvage rate	21/25 (84%)	18/25 (72%)
Mortality	1/25 (4%)	2/25 (8%)

We believe CDT provides a reasonable safe adjunct or alternative in this subset of patients. As this is a retrospective study, we have not been able to compare results of CDT in autogenous vein grafts as this was not the practice of the surgeons at the time. However, there is some literature to suggest the results of CDT are similar in occluded autogenous veins, innate vessels as well as prosthetic grafts.[15] Our study continues to corroborate the high initial technical success rate which has been shown by other studies (80%).[15–18] In almost all cases when CDT was not successful, these patients had un-reconstructable distal disease and proceeded to amputation. CDT not only cleared the thrombus from grafts but also demonstrated when the distal circulation could not be reopened as a result of progressive distal disease. This often made management decisions more straightforward.

One of the main criticisms of those that oppose the use of CDT is the perceived incidence of serious haemorrhagic complications. Cursory inspection would suggest that our degree of technical success has been followed by a significant bleeding complication rate (16%). In all cases, these were bleeding at the puncture site. There was a direct correlation between the size of incision made for vascular access and the degree of bleeding. Adjunctive surgical procedures accounted for 50% of post-CDT major bleeding complications. Adjunct surgery should therefore be avoided where possible. Revascularisation of critically ischaemic limbs is always associated with the risk of compartment syndrome, no matter which technique is used. This is demonstrated in our study which shows the incidence of fasciotomies to be 8%. The only graft infection associated with our study occurred after amputation following CDT failure with infection in the residual graft which needed to be removed subsequently. We do not believe this was a direct complication of CDT. Pre-angiography antibiotic prophylaxis may minimise the risk of infection.

Though some other studies have suggested the maturity of grafts was a factor in CDT success, especially in relation to patency rates,[19] no statistical difference was seen in both the immediate technical success rates and secondary patency rates between the subgroups examined in our study. As our study is quite small, this may be a type II error. An underlying lesion was unmasked in 60% of cases, which is comparable to previous reports in comparable studies.[15,16,18] Dealing with these is crucial to the overall patency of the grafts. Pedersen et al.[20] suggested that the failure to find an underlying stenosing lesion was a poor prognostic indicator. The most prevalent lesion in our study was a distal stenosis (66.6%), which is in keeping with findings from other series and may be

responsible for graft failure. However, there is a significant finding of proximal lesions too (33.3%) which occurred either in isolation or in combination with a distal lesion. Interestingly, there were no intra-graft lesions, which may suggest they play very little role in the occlusion of prosthetic grafts. Brumberg et al.[21] suggested that low flow within the graft may be a more important duplex predictor of graft failure. Distal stenosis, peripheral progression of atherosclerosis and significant proximal stenosis (in order of importance) would all lead to a low flow state within the graft and could be the final common pathway of graft failure. Thus, surveillance with duplex ultrasound and documentation of low slow rate within the graft should play an important role in the management of these grafts. Demonstration of a low flow may then suggest a role for warfarin as suggested by Brumberg et al.[21]

As demonstrated in this study, angioplasty can be done successfully for the graft associated stenosis, but distal disease is often the cause of failure and eventual limb loss. Limb salvage was 72% at one year which is comparable to previous findings. However, all of these had clearly progressive distal disease and it is unlikely that these limbs could have been saved in any other way. With careful patient selection, failed CDT would mean that patients are inappropriate for any other limb saving procedure. Theoretically CDT might prolong the time to complete outlet failure by opening up thrombosed distal vessels, thus prolonging the time to limb loss. This might be crucial in elderly patients where the loss of independence from limb loss could be devastating.

The secondary patency rates in our study (76.5% at nine months) are better than reported in other studies and we think this is due to the aggressive attention paid to ensuring adequate run-off by angioplasty during CDT.[15,16,20] Patency was ensured by repeated CDT ± angioplasty ± proximal stents as required over the ensuing 12 months. Failure was always because of progressive distal disease and two of these went on to lose their limbs. An analysis of the long-term patency rate in this cohort of patients would be useful. However, our study shows that CDT is not associated with the poor patency rates previously reported. We suspect these rates will continue to improve as techniques and use of CDT develops. Furthermore patency rate on its own is argued to be a poor measure of success in limb reperfusion. As these occluded grafts initially present with a threatened ischaemic limb, a better measure of success would be limb salvage. It is clear that though some of the grafts re-occlude after CDT limb loss is not inevitable. We feel that CDT is able to prolong limb viability, even when the graft has re-occluded.

The one year mortality rate in our group of patients was 8% (2/25), but none of these deaths were directly related to CDT. One patient died after surgery to re-vascularise his limb failed, and was followed by multiorgan failure. The other would have died irrespective of any surgical intervention as he was unsuitable for surgery and developed massive rhabdomyolysis when CDT failed. Critical limb ischaemia is associated with a one year mortality rate of over 25%[22] and the above mentioned mortality rate in our group of patients would therefore be acceptable. It is debateable whether accepting a limb loss in the first patient would have resulted in a better mortality rate. Surgery is not without its risks and CDT may be a better alternative in some circumstances.

5. Conclusions

CDT can achieve reasonable results in this group of difficult patients and should be seen as a useful accessory in the vascular toolkit. However, the exact indications for its use need further clarification.

Ethical approval

None.

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Nil.

Author contribution

CUAI contributed to study design, data collection and analysis as well as writing of the paper. MRSS contributed to analysis and writing of the paper. LTG, JH, NB contributed to writing of the paper and design.

Conflicts of interest

Nil.

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